



Flash pulmonary oedema and bilateral renal artery stenosis: the Pickering Syndrome[†]

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Introduction

In 1988 Pickering *et al.* reported in the *Lancet* a series of 11 hypertensive patients with bilateral atheromatous renovascular disease who presented with a history of multiple episodes of pulmonary oedema.¹ Seven of these patients had stenosis of both renal arteries and in a subsequent series of 90 patients, pulmonary oedema was significantly more common in patients with bilateral than in those with unilateral renal artery stenosis (RAS).² Successful revascularization of one or both renal arteries eliminated pulmonary oedema in 77% of patients with bilateral RAS.² The authors concluded that 'bilateral RAS may be a specific and treatable predisposing factor to pulmonary oedema in azotemic hypertensive patients'.¹ Since the initial observation of this clinical entity 29 case reports,^{3–31} 9 case series,^{1,32–39} and 10 clinical studies^{1–2,40–47} of flash pulmonary oedema (FPO) and RAS (both unilateral and bilateral) have been published of which 16 case reports, 2 case series, and 7 clinical studies comprising a total of 87 patients relate to bilateral RAS and FPO. The underlying pathophysiological mechanisms responsible for triggering FPO in patients with bilateral RAS have been delineated in several clinical and experimental studies. Since FPO and bilateral RAS seem to be a unique entity with distinct pathophysiological, clinical, and therapeutic features, we propose to name it Pickering Syndrome. In the following, we review incidence, pathophysiology, clinical findings, and treatment of the Pickering Syndrome.

Definition

Flash pulmonary oedema is a general term used to describe a particularly dramatic form of acute decompensated heart failure. Regardless of its aetiology, an acute increase of left ventricular (LV) end diastolic pressure is the *conditio sine qua non* for the development of FPO and remains the common denominator of

all clinical situations associated with it. However, what distinguishes FPO from other forms of decompensated heart failure is that because of unique underlying pathophysiological mechanisms, flooding of the alveolar space can occur within minutes resulting in an acute life-threatening emergency.⁴⁸

Prevalence

Atherosclerotic renal artery disease is increasingly diagnosed and strongly associated with atherosclerotic disease in other vascular beds such as the coronary, carotid, and iliofemoral circulation.⁴⁹ Renovascular hypertension is the most common secondary cause of hypertension. In 26 studies comprising a total patient population of 30 092 undergoing diagnostic coronary angiography for suspected coronary artery disease the prevalence of RAS >50% averaged 8.0% with a range from 3.1 to 22.9% (*Table 1*).^{43,50–74} Of all patients with atherosclerotic RAS, 20.3% had significant bilateral RAS. The prevalence of FPO varies a great deal and seems to depend on the pressure load as well as on the degree of renal impairment. In a series of 56 patients with bilateral RAS, Bloch *et al.*² reported a history of FPO before revascularization in 23 (41%) patients. Messina *et al.*³⁵ reported 17 patients with RAS treated at the University of Michigan Hospital, 16 of who had bilateral disease. Mean blood pressure was 207/110 mmHg and serum creatinine was 3.5 mg/dL. Two-thirds of these patients had FPO despite evidence of normal ventricular function. Overall the weighted prevalence of FPO in patients with RAS was 15.3%. In patients with bilateral RAS the weighted prevalence of FPO was 14.3% compared with 3.5% in those with unilateral RAS.

Pathophysiology

Bilateral RAS predisposes patients to develop FPO by three main pathophysiological mechanisms: (i) defective natriuresis;

[†]Thomas G. Pickering passed away on 14 May 2009 after a short battle with a brain tumour.

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Table 1 Prevalence of RAS >50% in patients undergoing cardiac catheterization

Study	Year	Number of patients	Prevalence of RAS (%)	Prevalence of bilateral RAS ^a (%)
Alhaddad et al. ⁵⁰	2001	171	7.60	38.5
Aqel et al. ⁵¹	2003	90	27.8	36
Buller et al. ⁵²	2004	851	14.1	—
Cohen et al. ⁵³	2005	843	18.3	—
Conlon et al. ⁵⁴	2001	3987	9.10	—
Crowley et al. ⁵⁵	1998	14 152	6.20	20.2
Dzielińska et al. ⁵⁶	2007	333	12.0	20
Ghaffari et al. ⁴³	2009	732	11.9	42.5
Harding et al. ⁵⁷	1992	1235	15.2	27.7
Jean et al. ⁵⁸	1994	196	18.4	—
Leandri et al. ⁵⁹	2004	467	9.00	31
Ollivier et al. ⁶⁰	2009	650	14.5	21.3
Ramirez et al. ⁶¹	1987	102	4.90	—
Ravichandran et al. ⁶²	2003	614	8.47	9.6
Rigatelli et al. ⁶³	2005	205	19.5	37.5
Rihal et al. ⁶⁴	2002	297	19.2	19.3
Rimoldi et al. ⁶⁵	2010	1403	8.00	25
Saleh and Bustami ⁶⁶	2004	354	3.10	18.2
Sani et al. ⁶⁷	2008	260	14.2	—
Shen et al. ⁶⁸	2001	280	15.4	32.6
Song et al. ⁶⁹	2000	427	5.60	25
Tumelero et al. ⁷⁰	2005	1656	13.7	11
Vetrovec et al. ⁷¹	1989	118	23	37
Wang et al. ⁷²	2003	203	14.8	16.7
Weber et al. ⁷³	2002	177	10.7	26.3
Yamashita et al. ⁷⁴	2002	289	7.3	14.3
Total		30 092	8.0	20.3

^aPrevalence of bilateral RAS as % of all RAS patients. RAS, renal artery stenosis.

(ii) increased haemodynamic burden and exacerbation of diastolic dysfunction;⁷⁵ and (iii) failure of the pulmonary capillary blood–gas barrier (Figure 1).

Experimental studies allow us to clearly delineate differences in pathophysiology between unilateral and bilateral RAS. In patients with unilateral RAS corresponding to the 2-kidney-1-clip hypertension model, stenosis of one renal artery decrease ipsilateral renal perfusion thereby activating the renin–angiotensin–aldosterone cascade and causing sodium and fluid retention.⁷⁶ Concomitantly, stimulation of the sympathetic nervous system occurs, triggered directly by renal ischaemia⁷⁷ as well as by the activation of the renin–angiotensin system.⁷⁸ Since the contralateral kidney is functioning normally, it compensates for the increase in blood pressure by suppressing renin secretion and augmenting sodium excretion; so-called pressure natriuresis occurs. However, this escape mechanism is defective in patients with bilateral RAS which corresponds to the 1-kidney-1-clip hypertension model. Since now perfusion to both kidneys is hampered, pressure natriuresis cannot take place and intravascular volume expansion secondary to sodium and water retention persists.⁷⁹ Indeed, Hall et al.⁸⁰ experimentally showed that high circulating angiotensin levels caused a marked increase in blood pressure and sodium retention, rapidly resulting

in FPO when renal artery perfusion pressure was kept low, as is the case with bilateral RAS. In contrast, no sodium retention was observed when renal artery pressure was allowed to increase, suggesting that this increase is seminal in helping the kidneys to escape from the sodium retaining effect of angiotensin.

Sustained blood pressure elevation in patients with RAS may give rise to left ventricular hypertrophy (LVH) most often of the concentric type and to diastolic LV dysfunction.⁸¹ Concomitant arterial stiffening increases pulse wave velocity so that the reflected pulse wave returns during systole instead of during diastole^{82–83} thereby further augmenting systolic ventricular pressure load.⁸⁴ Normally, the LV compensates for an increase in afterload by increasing end-diastolic volume (preload reserve). However, in patients with a stiff LV, this safety mechanism is rapidly exhausted and even small increases in LV end-diastolic volume may give rise to a marked elevation in end-diastolic pressure, left atrial, and pulmonary venous pressure.⁷⁸ Moreover, in patients with diastolic dysfunction and stiff LV, excessive sympathetic activation may also precipitate the development of FPO. The tachycardia-induced decrease of diastole duration further impairs the ability of the stiff LV to fill and results in retrograde elevation of pulmonary venous pressure. Hence, patients with LV and vascular stiffening

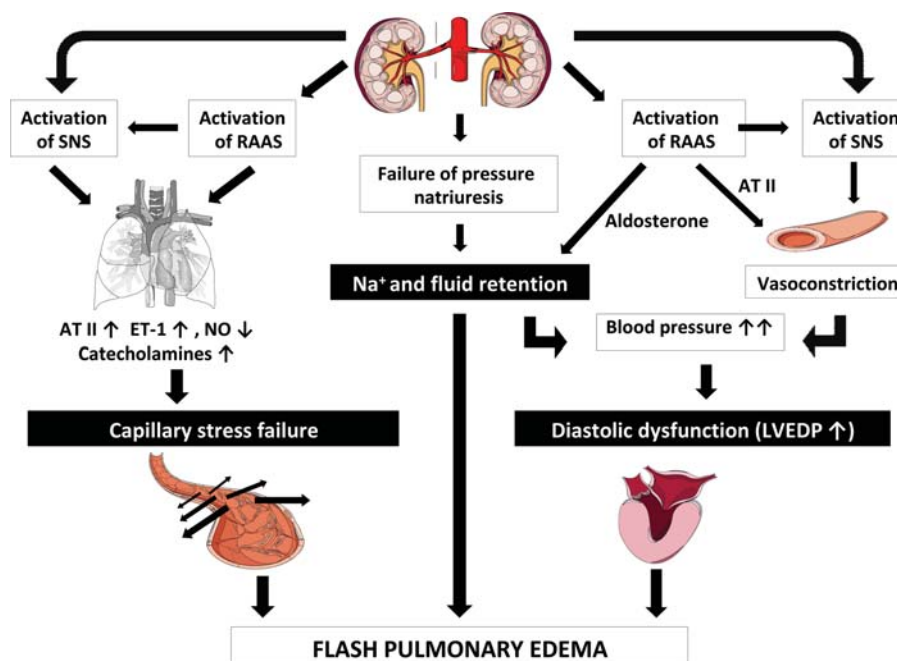


Figure 1 The Pickering Syndrome. Three main pathophysiological mechanisms contribute to the development of flash pulmonary oedema: defective pressure natriuresis with sodium and fluid retention, increased left ventricular end-diastolic pressure associated with left ventricular hypertrophy and stiffening, and failure of the pulmonary capillary blood–gas barrier. RAAS, renin–angiotensin–aldosterone system; SNS, sympathetic nervous system; Na^+ , sodium; All, angiotensin II; ET-1, endothelin-1; NO, nitric oxide.

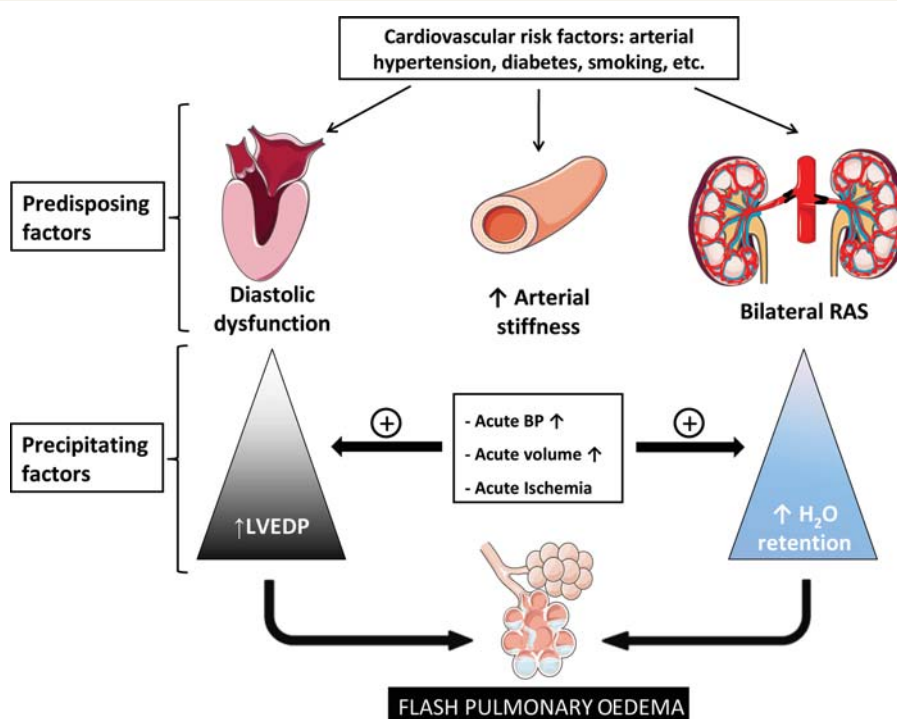


Figure 2 Key predisposing (left ventricular diastolic dysfunction, increased arterial stiffness, bilateral renal artery stenosis) and precipitating (acute increase in blood pressure and/or intravascular volume, acute myocardial ischaemia) factors of the Pickering Syndrome. RAS, renal artery stenosis. LVEDP, left ventricular end-diastolic pressure.

have an exaggerated response to changes in intravascular volume and sympathetic activity.⁸⁵ Furthermore, the increased systemic vascular resistance secondary to activation of renin angiotensin aldosterone cascade and sympathetic nervous system increases LV wall stress and causes a mismatch between increased oxygen demand and delivery to the myocardium. This, in turn, aggravates LV diastolic dysfunction resulting in a further increase in LV end-diastolic pressure (Figure 1).

Pulmonary capillary stress failure and increased pulmonary vascular permeability are important but often overlooked pathogenetic mechanism of FPO.⁴⁸ The rapid and exaggerated increase in LV pressure transmits to left atrium, pulmonary veins and to the unprotected pulmonary capillaries. Once intracapillary pressure exceeds 20–25 mmHg the oedema fluid leaks through the endothelial barrier and floods the interstitial and, subsequently, alveolar space.⁴⁸ Excessive plasma and tissue levels of neurohumoral mediators, such as angiotensin II, catecholamines, and endothelin-1, may increase permeability of the alveolo-capillary barrier.⁴⁸

In the case of decompensated bilateral RAS all of the above-mentioned predisposing factors reunite and overcome the protective mechanisms against alveolar fluid accumulation. In this precarious situation even small fluctuations in blood pressure, intravascular volume or renal perfusion and/or myocardial ischaemia may act as precipitating factors that can trigger FPO (Figure 2).⁴⁸ Once FPO ensues, LV pump function is prone to decline which, in turn, will further hamper perfusion of the kidneys, thereby giving rise to a vicious circle.

Clinical findings

The Pickering Syndrome can present a diagnostic conundrum and the clinical findings of bilateral RAS must be differentiated from unilateral RAS (Table 2). In the series described by Pickering, FPO occurred on average 2.3 times before a diagnosis of RAS was established. In our literature review of 87 patients with the Pickering Syndrome mean age was 63 years, 47% were male and 73% were smokers. Of these patients 58% had coronary artery

disease and 40% had heart failure diagnosed in the past. Average ejection fraction was 49% and 50% had LVH. Renal failure was evident in 94% of patients and the mean creatinine was 3.8 mg/dL (336 µmol/L). As to FPO, only 7% had a single episode of FPO before the diagnosis and 93% had recurrent episodes of FPO. Classically, patients present with sudden onset of severe, unprovoked dyspnoea ('flash' pulmonary oedema) although the LV systolic function is usually normal. The occasional presence of coronary artery disease may result in misinterpretation of FPO as being caused by coronary ischaemia. However, in many patients, coronary angiography reveals no flow limiting stenosis. This finding coupled with normal LV systolic function can lead to a false sense of security or give rise to evaluation for non-cardiac causes for dyspnoea. The frequent nocturnal appearance of FPO may be due to reverse nocturnal dipping which has been well documented in patients with RAS.^{86,87}

Therapy

The therapeutic approach to the Pickering Syndrome can be divided into two distinct phases.

Phase 1 is characterized by the occurrence of FPO which represents a hypertensive emergency requiring immediate therapeutic intervention. Haemodynamic unloading by antihypertensive drugs usually result in prompt resolution of FPO but may further compromise renal blood flow and function. This is particularly true with inhibitors of the renin–angiotensin–aldosterone system. Although empirically, renin–angiotensin–system inhibitors should prove to be very useful for emergency treatment of FPO, they may precipitate acute renal failure and their continued use becomes relatively contraindicated once the patient has been stabilized. In the acute phase, a loop diuretic should be added to initiate natriuresis and overcome sodium retention. Of note, there is no iron clad evidence to exactly guide us, how to optimally proceed in a patient presenting with the acute phase of the Pickering Syndrome. In Phase 2, once the patient is out of pulmonary oedema and has been stabilized, renal revascularization is the treatment of choice, since the pathophysiology of the Pickering Syndrome is characterized by the inability to generate a pressure natriuresis due to renal hypoperfusion.^{2,47} Both surgical and percutaneous revascularization techniques have been successful in treating RAS and its clinical manifestations such as FPO (Table 3).^{1–2,32,35–36,38,44–45,88–90} Renal revascularization decreases circulating angiotensin and aldosterone levels resulting in a fall in blood pressure, and since revascularization improves renal perfusion, in an increase in glomerular filtration rate and natriuresis.

Renal artery surgery is an effective method for revascularization but is associated with greater morbidity and mortality than percutaneous endovascular techniques. The ACC/AHA guidelines endorse percutaneous revascularization as a class I recommendation for patients with haemodynamically significant RAS and recurrent, unexplained congestive heart failure, or pulmonary oedema.⁹¹ The efficacy of successful renal artery revascularization in resolving FPO can be dramatic (Table 3). Evidence is compelling that stenting is superior over balloon angioplasty.^{91–93} This is particularly true for atherosclerotic aorta-ostial RAS.^{94–96} In patients with severe/acute heart failure and combined renovascular and coronary artery disease, renal revascularization with stents

Table 2 Differences in clinical findings before unilateral and bilateral renal artery stenosis

	Renal artery stenosis	
	Unilateral	Bilateral
RAAS activation	↑↑	↑
Na/Fluid volume state	Pressure natriuresis	Sodium retention
Cardiac output	Normal	↑
Total peripheral resistance	↑↑	↑
BP response to RAS blockade	↑↑	↑
Flash pulmonary oedema	Rare	Common
Natriuresis post angioplasty of RAS	No	Yes

BP, blood pressure; RAAS, renin–angiotensin–aldosterone system; RAS, renal artery stenosis.

Table 3 Responders to revascularization as reported in various studies

Study	Patients	Bilateral RAS	Unilateral RAS	Surgery	Balloon	Stent	Responders (%)
Bloch <i>et al.</i> ²	25	22	3	0	0	25	72.0
Diamond ³²	3	3	0	3	0	0	66.0
Gray ⁸⁸ 2002	39	39	0	0	0	39	77.0
Kane ⁸⁹ 2010	50	27	23	0	0	50	88.0
Khosla ⁴⁴ 1997	28	20	8	0	0	28	85.7
Messina <i>et al.</i> ³⁵	17	16	1	16	1	0	100.0
Missouri ⁹⁰	9	5	4	1	8	0	100.0
Pelta <i>et al.</i> ⁴⁵	8	4	4	0	0	8	88.0
Pickering ¹	11	9	2	3	8	0	90.9
Planken and Rietveld ³⁶	2	2	0	0	2	0	100.0
Weatherford ³⁸	5	5	0	5	0	0	100.0

RAS, renal artery stenosis.

achieves similar outcomes and improved functional status independent of coronary revascularization.⁴⁷ A recent cohort-controlled study demonstrated a significant benefit for renal stent revascularization compared with continued medical therapy in 50 patients presenting with heart failure who had bilateral RAS or RAS and a solitary kidney being treated for uncontrolled hypertension or ischaemic nephropathy.⁸⁹ Patients who received renal stents improved their New York Heart Association Functional Class (1.9 ± 0.8 vs. 2.6 ± 1.0 , $P < 0.04$) compared with those treated conservatively. Although there was no mortality benefit, there was a significant reduction in recurrent heart failure events and the need for rehospitalization was reduced five-fold in the renal stent group. Renal stenting has a remarkably low failure rate with primary patency rates of 79–84% and secondary patency rates of 92–98% after 5 years of follow-up.^{97,98}

In our literature review of 87 reported cases of bilateral RAS and FPO, 35% were treated with unilateral and 22% with bilateral angioplasty. In 43% of patients, mostly in earlier reports, surgical revascularization was performed. Stenting was unsuccessful in two patients, one of whom improved with carvedilol and the other after resuming ACE-Inhibitor therapy. Renal function improved in 81% of patients and the mean creatinine on follow-up was 1.6 mg/dL ($141 \mu\text{mol/L}$) after the procedure. Renal function was normal at baseline and after angioplasty in two patients only. Importantly, in 92% of all patients there was no further episode of FPO after revascularization.

The acute phase the Pickering Syndrome can be treated effectively by haemodynamic unloading and diuresis. In the subacute phase renal stenting is treatment of choice. However, long-term prognosis in patients with bilateral RAS remains guarded. Conlon *et al.*⁵⁴ reported a 4-year survival rate of <50% in a series of 33 patients.

Comments

The Pickering Syndrome must be considered a unique pebble in the mosaic of the so-called cardiorenal syndrome, a pathophysiological condition in which impairment of cardiac and renal function mutually accelerates each other. However, in contrast to the

cardiorenal syndrome which is ill defined and has a somewhat nebulous pathophysiology, the Pickering Syndrome is clearly defined and its pathophysiological mechanisms have been precisely delineated. As such it is prone to serve as an illuminating teaching model shedding light on one straight forward aspect of the complex interaction between heart and kidney. This brings us back to Thomas Pickering who dedicated his career in cardiovascular medicine to research, teaching, and patient care. His original paper in *Lancet*¹ is a prime example of keen observation and crystal clear thinking attesting to his preeminence as an astute teacher and clinician.

A personal memoir

Tom Pickering was one of my first D.Phil students in Oxford in the late 1960s, following Harley Smyth in the early studies of the cardiovascular effects of sleep in man. He was quietly modest, but an outstandingly able and intelligent person, a pleasure to work with—even during the middle of the night! His Oxford thesis on 'Baroreceptor reflexes in man in health and disease' was published in 1970 and resulted in a series of publications in high-impact journals. I tried hard to get him to stay in Oxford, but could understand his wish not to stay there—where his famous father was Regius Professor of Medicine. He made his name in New York with seminal work describing the psychological influences on cardiovascular disease, with thoroughly controlled studies of the effects of different kinds of job stress on blood pressure. The importance of psycho-social influences on cardiovascular disease is now well recognized and has become academically respectable—in large part due his work. I was immensely impressed with the way Tom managed himself when knowing he had limited time left. Supported bravely by his wife Janet, he came to several European meetings in his final year, giving papers and joining discussions as if nothing was amiss (P.S.).

Conflict of interest: none declared.

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